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THERAPEUTIC ADVANCES in
Infectious Disease

Meta-analysis

Microbiological characterization of bacteremia in patients with chemotherapy-induced febrile neutropenia: systematic review and meta-analysis

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Abstract

Background: Febrile neutropenia (FN) is the most common and serious adverse event of chemotherapy for solid and hematological neoplasms, with infection as a major complication. FN occurs in 10%–50% of patients with solid tumors and over 80% with hematological malignancies, with mortality rates up to 11%.

Objective: To characterize bloodstream pathogens in post-chemotherapy FN through a systematic review and meta-analysis of studies published from 2013 to February 13, 2024.

Design: Systematic review and meta-analysis.

Data sources and methods: PubMed, Web of Science, Scopus, and Embase were searched using MeSH, Emtree, and keywords. Risk of bias was assessed using the JBI checklist. Random-effects proportions meta-analysis was performed.

Results: Twenty-two studies ($n = 23{,}319$) reported 8665 positive blood cultures: 59% Gram-negative (95% CI: 46.8–67.5), 39.7% Gram-positive (95% CI: 31.3–48.2), and 2.5% fungi (95% CI: 0.9–4.1). Random-effects meta-analysis showed high heterogeneity ($I^2 = 98.92\%$, $p < 0.01$). Meta-regression by sample size, economic development, and risk of bias did not explain this variability.

Conclusion: Gram-negative pathogens slightly predominate over Gram-positives in bloodstream infections among post-chemotherapy FN patients.

Trial registration: PROSPERO (CRD42023472191).

Plain language summary

Understanding blood infections in cancer patients with low white blood cell counts: a review and analysis

The study highlights the significant prevalence of pathogens in the bloodstream of patients experiencing febrile neutropenia (FN) after chemotherapy. It identified a total of 21,485 patients from 23 studies, revealing that 46.1% of positive blood cultures were Gram-negative bacteria, while Gram-positive bacteria accounted for 45.6%. Additionally, fungi represented only 1.9% of the pathogens. The systematic review and meta-analysis showed considerable heterogeneity among the studies, indicated by an I^2 of 98.92%.

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Despite evaluating various factors such as sample size, economic development, and risk of bias, none significantly influenced this heterogeneity. In conclusion, the findings suggest that Gram-negative bacteria are slightly more prevalent than Gram-positives in cases of FN following chemotherapy, underscoring the need for targeted antimicrobial strategies in this vulnerable patient population.

Keywords: bacteremia, epidemiology, febrile neutropenia induced by chemotherapy, fungemia, sepsis

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Introduction

Cancer remains a leading global cause of death, with nearly 10 million deaths and 20 million new cases in 2020.[1] Chemotherapy is central to treating both solid and hematologic malignancies.[2,3] Febrile neutropenia (FN) is one of the most common and severe adverse effects of chemotherapy. FN is defined as a single oral temperature measurement of ⩾38.3°C (101°F) or ⩾38.0°C (100.4°F) sustained for more than 1 h, in patients with an absolute neutrophil count (ANC) of <500 cells/μL or expected to decrease to <500 cells/μL within 48 h.[4,5] FN often necessitates hospitalization and broad-spectrum antibiotics,[4,5] and is associated with increased mortality, healthcare costs, and delays or modifications in cancer treatment.[4,5]

FN occurs in 10%–50% of patients with solid tumors and over 80% of those with hematologic malignancies receiving chemotherapy.[6] It significantly increases the risk of serious infections, particularly bloodstream infections (BSIs), which contribute substantially to morbidity and mortality in this population. Patients with FN have an estimated 15% higher risk of death compared to those without FN.[7]

The epidemiology of BSIs in FN patients has shifted over time.[9] While Gram-positive organisms predominated in the late 20th century, the past two decades have seen a resurgence of Gram-negative pathogens, likely driven by evolving chemotherapy regimens, antimicrobial use, and invasive procedures such as central venous catheterization.

Despite advances in FN management and prophylactic strategies, current data on BSI pathogens in post-chemotherapy FN remain fragmented, varying across regions and time periods. No clear consensus exists on the predominant microbial etiology, complicating efforts to standardize empiric therapy and prevention protocols. Discrepancies in trends—such as the resurgence of Gram-negatives—further hinder the development of universal treatment guidelines.

This study aims to systematically review and synthesize evidence on the distribution and characteristics of the pathogens causing BSI in adult patients with post-chemotherapy FN. Understanding these trends is crucial to inform empirical treatment, guide prophylaxis, and ultimately reduce FN-related morbidity, mortality, and healthcare burden in cancer patients.

Materials and methods

This study adheres to the Preferred Statement Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020)[10] and was previously registered with PROSPERO (ID number: CRD42023472191).

Study design

Systematic Review and meta-analysis were conducted and reported in accordance with the PRISMA guidelines.[10]

Eligibility criteria

Primary studies on bacteremia in post-chemotherapy neutropenic patients, aged 18 years, published between 2013 and February 13, 2024, without language restrictions, were included. Exclusion criteria comprised studies involving COVID-19, pediatric or pregnant populations, non-chemotherapy-related febrile neutropenia, as well as review articles, letters to the editor, case reports, and conference abstracts.

Sources of information

A comprehensive search was conducted in PubMed, Web of Science, Scopus, and Embase using MeSH and Emtree terms (e.g., *Neoplasms*, *Hematologic Neoplasms*, *Bloodstream Infection*, and *Prevalence*), as well as free-text terms (e.g., *cancer*), combined using Boolean operators (AND, OR). The search strategy was tailored to each database (see Supplemental Material).

Eligibility assessment

Eligibility assessment was conducted independently and blinded by two reviewer pairs (FC-PG and FG-HA). Discrepancies were resolved by consensus. Article selection was finalized on February 13, 2024.

Data extraction

Data was extracted using a standardized Excel spreadsheet (Microsoft Excel, version 15.24; 2016). Two authors (FC and PG) extracted data from the included studies, and three others (FG, YYL, and HA) verified the data. Disagreements between reviewers were resolved by consensus.

Variables

The primary outcome was the prevalence of bloodstream infections. Secondary variables included tumor type, bacteria classification (Gram-positive or Gram-negative), specific pathogens, antimicrobial resistance, infection management, and the occurrence of sepsis or septic shock. Additional extracted data included study design, year of publication, country, sample size, FN diagnostic criteria, study period, number of centers, and funding source. Definitions of febrile neutropenia used by each author can be seen in Tables 1 and 2.

Study risk of bias assessment

The risk of bias was assessed independently by two reviewers (AF-C, PG) through the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for studies reporting prevalence data.[11–13] This tool assesses nine domains where final scores were determined based on the percentage of affirmative responses. Studies were classified as high risk of bias (score of 49% or less, leading to exclusion of the study), moderate risk (score ranging from 50% to 69%), or low risk (score above 70%). Discrepancies were resolved by consensus.

Risk of bias summaries were generated using the ROBVIS R package v.0.3.0.900.[14]

Data synthesis

Descriptive statistics (percentages, frequencies, and means) were used to summarize the data. A random-effects meta-analysis was performed using the Freeman-Tukey reverse transformation model. Studies with a high risk of bias were excluded. Heterogeneity was assessed using Cochran's Q test (significance set at $p < 0.05$) and the I^2 statistic. Univariate meta-regression was performed using the covariates: risk of bias, sample size, and Country Development Status.

Sensitivity analyses included subgroup analysis assuming $I^2 = 10\%$, leave-one-out meta-analysis, and standard error adjustments using the Sidik-Jonkman and truncated Knapp-Hartung methods. All analyses were performed using Stata 18 statistical software (StataCorp LLC, College Station, TX, USA).

Reporting bias assessment

To assess small-study effects, funnel plots were generated, and Egger's test was performed for studies reporting Gram-negative, Gram-positive, and fungal infections. A $p < 0.05$ was considered statistically significant. Trim-and-fill analysis was performed to determine if imputed studies affected the effect size.

Assessment of certainty

It was not considered.

Ethics

Secondary evidence does not require the authorization of an Institutional Review Board; thus, ethics approval was not considered.

Results

A total of 7630 articles were identified across the databases. After removing duplicates and screening titles and abstracts, 266 articles were retained

Table 1. Characteristics of the studies included in the systematic review.

Author	Year	Type of study	Country	Study period	Population	Number of centers	Definition of neutropenic fever	Financing
De Rosa[15]	2013	Retrospective	Italy	June 2001–December 2007	81	1	ANC ⩽ 500/mm^3 and external temperature ⩾ 38°C	Turin Hospital
Bousquet[16]	2014	Retrospective	France	2003–2010	1413	1	ANC ⩽ 500/mm^3 and external temperature ⩾ 38°C	N/R
Rosa[17]	2014	From Prospective Cohort	Brazil	October 2009–August 2011	307	1	ANC ⩽ 500/mm^3 or with expectation of decreasing to < 500 mm^3 over 48 h and external temperature ⩾ 38°C or sustained temperature of ⩾ 38.0°C over a 1-h period	APIC
Mandal[35]	2015	Prospective	India	September 2010–October 2013	268	1	ANC ⩽ 500/mm^3 and external temperature ⩾ 38°C or sustained temperature of ⩾ 38.0°C over a 1-h period	N/R
Marin[36]	2015	Prospective Observational	Spain	January 2006–December 2013	602	1	ANC ⩽ 500/mm^3 and external temperature ⩾ 38°C	N/R
Piukovics[18]	2015	Retrospective Observational	Hungary	2005–2008	469	1	Single oral temperature was measured higher than 38.3°C, or temperature was 38.0°C or higher for 1 h. ANC < 0.5 × 10^9/L or less than 1.0 × 10^9/L and rapidly declined below 0.5 × 10^9/L	N/R
Cattaneo[19]	2016	Prospective Observational	Italy	December 2010–December 2014	293	9	PMN count < 0.5 × 10^9/L; axillary temperature ⩾38.3 or ⩾ 38°C for a least 1 h	None
Rönkkö[20]	2018	Prospective and compared with a retrospective series	Finland	December 2006–November 2012	178	1	ANC ⩽ 500/mm^3 and external temperature ⩾ 38°C or sustained temperature of ⩾ 38.0°C over a 1-h period	N/R
Zhu[21]	2018	From cohort Retrospective	China	January 2005–December 2012	1139	1	ANC ⩽ 500/mm^3	Shanghai Science and Technology Committee, National Natural Science Foundation of China and MSD

(Continued)

Table 1. (Continued)

Author	Year	Type of study	Country	Study period	Population	Number of centers	Definition of neutropenic fever	Financing
Garzón[22]	2019	Retrospective Observational	Colombia	January 2013–December 2014	193	1	ANC $\leqslant$ 500/mm^3 and external temperature $\geqslant$ 38°C or sustained temperature of $\geqslant$ 38.0°C over a 1-h period	San Ignacio University Hospital
Herrera[23]	2019	Retrospective Observational	Argentina	June 2015–August 2017	32	1	ANC $\leqslant$ 500/mm^3 or with expectation of decreasing to $<$ 500 mm^3 over 48 h and external temperature $\geqslant$ 38°C or sustained temperature of $\geqslant$ 38.0°C over a 1-h period	N/R
Kim[24]	2019	Retrospective Observational	South Korea	June 2012–June 2018	179	1	Single oral temperature was measured higher than 38.3°C, or temperature was 38.0°C or higher for 2 h. ANC $\leqslant$ 500/mm^3 or with expectation of decreasing to $<$ 500 mm^3 over 48–72 h	N/R
Mert[25]	2019	Retrospective	Türkiye	January 2012–December 2017	266	1	N/R	N/R
Widmer[26]	2019	Prospective	Germany, Austria, Switzerland	2002–2010	13.525	20	ANC $<$ 1000 $\times$ 10^9/L; AGC $<$ 500 $\times$ 10^9/L; AGC of 1000 $\times$ 10^9/L with an expected dop to $<$ 500 $\times$ 10^9/L	German Federal Ministry of Health
Jung[27]	2020	Retrospective Observational	South Korea	June 2012–December 2016	133	1	ANC $\leqslant$ 500/mm^3	N/R
Martinez[28]	2020	Prospective Observational	Spain	January 2006–January 2017	1615	2	ANC $\leqslant$ 500/mm^3 and external temperature $\geqslant$ 38°C or sustained temperature of $\geqslant$ 38.0°C over a 1-h period	Ministry of Health and Consumer Affairs, Carlos III Health Institute, and research grant from Merck Sharp and Dohme, Catalonia Support Agency
Finello[9]	2021	Retrospective	Argentina	April 2009–December 2016	143	2	Temperature was measured higher than 38.2°C, or temperature was 38.0°C or higher for 1 h. ANC $\leqslant$ 500/mm^3 or with expectation of decreasing to $<$ 500 mm^3 over 48 h	None

(Continued)

Table 1. (Continued)

Author	Year	Type of study	Country	Study period	Population	Number of centers	Definition of neutropenic fever	Financing
Caro[29]	2022	Retrospective	USA	June 2012–October 2019	121	1	Temperature was measured higher than 38.3°C, or temperature was 38.0°C or higher for 1 h. ANC ⩽ 500/mm^3 or 1000/mm^3 with expectation of decreasing to < 500 mm^3	Astellas Pharma and AbbVie
Schulz[30]	2022	From Prospective Cohort	Australia	September 2020–July 2021	61	1	ANC ⩽ 500/mm^3 or 1000/ mm^3 with expectation of decreasing to < 500 mm^3 in the next 2 days; Temperature was measured higher than 38.3°C, or temperature was 38.0°C or higher for 1 h or measured two times within 12 h, respectively	None
Zimmer[31]	2022	Observational Cross-sectional Prospective	USA	December 2016–May 2019	343	14	Temperature was measured higher than 38.0°C. ANC ⩽ 500/ mm^3 or with expectation of decreasing to < 500 mm^3 over 48 h	University of Nebraska Medical Center
Perez[32]	2023	Pre- to post quasi-experimental	Peru	October 2015–October 2022	93	1	ANC ⩽ 500/mm^3 or 1000/ mm^3 with expectation of decreasing to < 500 mm^3. Oral temperature was measured higher than 38.3°C, or temperature was 38.0°C or higher for 1 h or measured 2 times within 2 h.	Pfizer Peru
Schonardie[33]	2023	Case-control Retrospective	Brazil	January 2012–January 2021	1865	1	ANC ⩽ 500/mm^3 or 1000/mm^3 with expectation of decreasing to < 500 mm^3 within 48 h. Axillary temperature was measured higher than 38.3°C, or 38.0°C for 1 h	Porto Alegre Clinics Hospital Incentive Fund.

ANC, Absolute Neutrophil Count; N/R, Not Report.

Table 2. Characteristics of included studies on febrile neutropenia treatment, infection management, and isolated pathogens.

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
De Rosa[15]	2013	6 (7.4)	N/R	Standard induction chemotherapy ICE followed by post-remissional therapy with repeated consolidation courses with high-dose cytarabine (HDAraC)	IDSA	Oral itraconazole, Levofloxacin	Gram-positive: • *Staphylococcus epidermidis* • *Enterococcus faecium* • *S. mitis* • *Corynebacterium* spp. • MRSA • *S. hominis* • *Corynebacterium* spp. • *E. faecalis* Gram-negative • *E. cloacae* • *E. coli* • *Klebsiella pneumoniae* • *Pseudomonas aeruginosa* • *S. maltophilia* • *S. marcescens* • *Citrobacter*
Bousquet[16]	2014	N/R	N/R	N/R	IDSA	Broad-spectrum, empirical, Ciprofloxacin, Piperacillin, Tazobactam	• Streptococcaceae • Staphylococcaceae • GPC • Enterobacteriaceae • Non-fermenting • GNB
Rosa[17]	2014	N/R	N/R	N/R	Unspecified	Vancomycin	Gram-positive • Methicillin-resistant coagulase-negative staphylococci • Methicillin-resistant *S. aureus* • Vancomycin-resistant *E. faecalis* Gram-negative • *E. coli* ESBL • *K. pneumoniae* ESBL • *Enterobacter* spp. • *Serratia* spp.
Mandal[34]	2015	N/R	N/R	N/R	IDSA 1997 Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer	N/R, does indicate drug-resistant isolates, however	Gram-positive • MRSA • MSSA • CONS • *S. pneumoniae* • MR CONS • *S. viridians* Gram-negative • *Acinetobacter* spp. • *P. aeruginosa* • ESBL *E. coli* • *K. pneumoniae* • *Citrobacter koseri* • *C. freundii* • *Ralstonia paucula* • *C. neteri* • Non-Fermenting Gram-negative bacilli • *E. coli*

(Continued)

Table 2. (Continued)

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
Marin[35]	2015	H: 61 (12.1) S: 33 (36.3)	N/R	N/R	IDSA	Cefepime + amikacin	Gram-positive • Coagulase-negative *staphylococci* • *S. aureus* • MRSA • Viridans group *streptococci* • *S. pneumoniae* • *Enterococcus* spp. • Other Gram-negative • *E. coli* • *K. pneumoniae* • *P. aeruginosa* • *Enterobacter* spp. • Other • MDR Gram-negative bacilli • ESBL-producing Enterobacteriaceae • *S. maltophilia* • AmpC-producing Enterobacteriaceae • MDR *P. aeruginosa* Polymicrobial Anaerobes
Piukovics[18]	2015	N/R	N/R	N/R	IDSA ESMO 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer CLSI	Piperacillin-tazobactam, Cefepime, imipenem, meropenem, vancomycin	Gram-positive • Coagulase-negative staphylococci • *S. aureus* • *Enterococcus* spp • *P. acnes* • *Beta-hemolytic streptococci* • *S. pneumoniae* • Alfa-hemolytic streptococci • *Clostridium* spp. • Others Gram-negative • *E. coli* • *P. aeruginosa* • *Klebsiella* spp. • *Enterobacter* spp. • *Citrobacter* spp. • *S. maltophilia* • *Acinetobacter* spp. • *Fusobacterium* spp. • Others

(Continued)

Table 2. (Continued)

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
Cattaneo[19]	2016	37 (8.5) Gram-positive 6.7% Gram-negative 9.1%	N/R	N/R	IDSA 2011 Fourth European Conference on Infections in Leukemia American Society of Clinical Oncology Clinical Practice Guidelines	Cephalosporin, cefotaxime, ceftazidime, cefepime; piperacillin/tazobactam + amikacin	Gram-positive • *S. aureus* • CoNS • Viridans group streptococci • Enterococci • Others Gram-negative • Enterobacteria • *P. aeruginosa* • Other Polymicrobic Fungi • *C. parapsilosis* • *C. guilliermondii* • *C. tropicalis* • *Fusarium solani*
Rönkkö[20]	2018	Dec 2006–Nov 2012: 4 (2.8) 1996–2006: 9 (3.4)	N/R	BEAM BEAC HD-MEL Others	IDSA ACCP/SCCM SEPSIS-3 Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective 2002 Guidelines for the use of antimicrobial agents in neutropenic patients with cancer SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference	Empiric antimicrobial, Broad-spectrum beta-lactam + aminoglycoside, ceftazidime, tobramycin, vancomycin, trimethoprim/sulfamethoxazole, ciprofloxacin	Gram-positive • *S. epidermidis* • *E. faecium* • *S. mitis* • *S. haemolyticus* • *S. pneumoniae* • *S. viridans* • *S. salivarius* • *Gemella morbillorum* • Other Gram-positive coccus Gram-negative • *E. coli* • *P. aeruginosa* • *Klebsiella pneumoniae* • Other
Zhu[21]	2018	N/R	N/R	N/R	IDSA ESMO Updated Guidelines of the AGIHO of the DGHO	Imipenem, Meropenem, Amikacin, Cefoperazone-sulbactam, Piperacillin-tazobactam, Cefepime, Ampicillin, Ciprofloxacin, Trimethoprim-Sulfamethoxazole, Vancomycin, Linezolid, Teicoplanin, Cefazolin, Cefuroxime, Phosphonomycin, Methicillin, Rifapicin, Levofloxacin	• *P. aeruginosa* • *K. pneumoniae* • *Acinetobacter baumannii* • *S. maltophilia* • *E. faecalis* • *E. cloacae* • *E. faecium* • *S. haemolytic* • *S. aureus* • *S. epidermidis* • Other

(Continued)

Table 2. (Continued)

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
Garzón[22]	2019	N/R	N/R	HyperCVAD, RCHOP, HIDAC, 7×3, IDAFLAG, PETHEMA, MEC	IDSA	Cefepime, Piperacillin/ Tazobactam, Meropenem	• *E. coli* • *K. pneumoniae* • *S. aureus* • *S. epidermidis* • *E. faecalis* • *Enterococcus* Spp. • *Candida* spp. • *P. aeruginosa* • *A. iwoffii* • *Proteus* spp. • *Clostridium* spp. • *K. oxytoca* • *E. faecium* • *Aeromonas* spp. • Other Gram-negative *Staphylococci* coagulosa • *Salmonella* spp. • *C. freundii* • *S. pneumoniae* • *Burkholedoria cepacian* • *Aspergillus* spp. • *S. viridans* • *S. maltophilia* • *S. haemolyticus* • *S. marcescens* • *S. agalactiae* • *S. mitis* • *K. ascorbate* • *Moraxella catarrhalis* • *Bacteroides* spp. • Other/Undetermined
Herrera[23]	2019	15 (45)	N/R	N/R	Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer IDSA 2011 Fourth European Conference on Infectious in Leukemia	Methicillin, Antipseudonomic penicillin, cefalosporin, carbapenem, quinolone, vancomycin, beta-lactam, carbapenem	Gram-positive cocci • Negative *S. coagulase* • *Enterococcus* spp. • *Streptococcus* spp. Gram-negative bacillus • *K. pneumoniae* • *E. coli* • *Enterobacter* spp. • *Serratia* spp. • Others Non-fermenting Gram-negative bacillus • *Acinetobacter* spp. • *P. aeruginosa* • *S. maltophilia* Toxins for *C. difficile* Fungi Others

(Continued)

Table 2. (Continued)

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
Kim[24]	2019	28-day mortality: 51 (28.5) In-hospital mortality: 46 (25.7)	N/R	N/R	IDSA Surviving Sepsis Campaign ESMO Clinical Practice Guidelines American Society of Clinical Practice Guideline Update	Piperacillin/tazobactam, cefepime, ceftazidime and cefazolin.	• *E. coli* • Other strains, unspecified
Mert[25]	2019	71 (23.3)	N/R	N/R	IDSA NCCN Clinical Practice Guidelines in Oncology (2014)	Cefoperazone-sulbactam, Piperacillin-tazobactam, Meropenem, Cefoperazone-sulbactam + vancomycin, Piperacillin-tazobactam + teicoplanin, Meropenem + daptomycin, Linezolid, Colistin, Meropenem + teicoplanin	Gram-positive • *E. coli* • *K. pneumoniae* • *P. aeruginosa* • *E. cloacae* • *A. baumannii* • *A. hydrophila/caviae* • *Pseudomonas* spp. • *S. paucimobilis* • *K. oxytoca* • *S. maltophilia* • *Acinetobacter lwoffi* • *Proteus mirabilis* Gram-negative • *S. haemolyticus* • *Corynebacterium* spp. • *S. epidermidis* • *E. faecium* • *S. mitis* • *S. hominis* • *S. aureus* • *S. warneri* • *Kocuriakristinae* • *Staphylococcus* spp.
Widmer[26]	2019	No BSI: 266 (2.0) Early-onset BSI: 62 (3.9) Late-onset BSI: 94 (10.9)	N/R	Unspecified antineoplastic chemotherapy	CDC criteria for pathogenic bacteria from a single blood culture IDSA 2011 Fourth European Conference on Infectious in Leukemia	N/R	Gram-positive • Coagulase-negative staphylococci • *Enterococcus* spp. • *E. faecium* • *Streptococcus* spp. • *S. aureus* Gram-negative • *E. coli* • KES group • *P. aeruginosa* • *S. maltophilia* Anaerobes Fungi • *Candida* spp. • *C. albicans* • Non-albicans *Candida* spp.

(Continued)

Table 2. (Continued)

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
Jung[27]	2020	N/R	N/R	N/R	Surviving Sepsis Campaign Sepsis-3 ACCP/SCCM Consensus Infectious Diseases Society of America (IDSA) 2014 AGIHO Updated Guidelines Evidence-based Guidelines for Empirical Therapy of Neutropenic Fever in Korea SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference	Extended-spectrum penicillin/beta-lactamase inhibitors (piperacillin-tazobactam), cephalosporin (cefepime), cefazolin/ceftazidime combination, or meropenem	Gram-positive • *S. aureus* • *S. pneumoniae* • Beta-Hemolytic streptocci • Viridans group streptococci • *Enterococcus* spp. • *Corynebacterium* spp. • Other Gram-positive bacteria Gram-negative • *E. coli* • *Klebsiella* spp. • *P. aeruginosa* • *Enterobactar* spp. • *Acinetobacter* spp. • *Legionella pneumophila* • Other Gram-negative bacteria Anaerobic bacteria • Anaerobic Gram-negative bacteria • Anaerobic Gram-positive bacteria

Martinez[28]	2020	Total: 21%
		E. coli: 80 (21)
		Klebsiella spp: 33 (24)
		P. aeruginosa: 87 (35)
		S. maltophilia: 13 (39)
		CoNS: 31 (9)
		Enterococcus spp: 58 (28)
		S. aureus: 10 (13)
			N/R	N/R	IDSA
					2011 Fourth European Conference on Infections in Leukemia
					2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation
						Amikacin, cefepime, meropenem, vancomycin, piperacillin-tazobactam, and imipenem	Gram-positive
							• CoNS
							• *Enterococcus* spp.
							  ○ *E. faecium*
							  ○ *E. faecalis*
							• *S. aureus*
							  ○ Methicillin-resistant S. Aureus
							Gram-negative
							• *E. coli*
							  ○ ESBL
							• *P. aeruginosa*
							  ○ Multidrug-resistant
							• *Klebsiella* spp.
							  ○ ESBL
							• *Enterobacter* spp.
							• *S. maltophilia*
							Anaerobes
							Candida spp.

Finello[9]	2021	0–7 days: 33 (23.1) 8–30 days: 27 (18.9) 31–60 days: 9 (6.3) 61–90 days: 2 (1.4) 90 days: 71 (49.7)	N/R	N/R	IDSA CDC/NHSN Surveillance Definition of Healthcare-Associated Infection and Criteria for Specific Types of Infections in the Acute Care Setting New Diagnostic Criteria and Severity Assessment of Acute Cholangitis in Revised Tokyo Guidelines 2011 Fourth European Conference on Infections in Leukemia	Penicillin, Antipseudomonics, cefalosporin, carbapenem, aminoglucosides, fluoroquinolones	*S. aureus* Negative *S. coagulase* *E. coli* *K. pneumoniae* *P. aeruginosa* *A. baumannii*

(Continued)

Table 2. (Continued)

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
Caro[29]	2022	Hazard ratio: 0.98 (0.56–1.71)	N/R	7 + 3 (cytarabine + daunorubicin or idarubicin)	Antibacterial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guidelines update CTCAE 5.0 2011 International Consensus Criteria on Antimicrobial Resistance	N/R	Gram-positive • *S. aureus* • Coagulase-negative *Staphylococcus* • Enterococci • Viridans group Streptococci • Other Gram-negative • *E. coli* • *B. thetaiotomicron* • *P. aeruginosa* • *K. pneumoniae* • *S. maltophilia* • *H. parainfluenzae* • *A. baumanii*
Schulz[30]	2022	N/R	N/R	N/R	IDSA 2018 AGIHO and iCHOP guidelines (DGHO) on the management of sepsis in neutropenic cancer patients	N/R	Blood culture positive • *A. ursingii* • *E. cloacae* • *E. faecium* • *G. haemolysans* • *P. aeruginosa* • *Rothia mucilaginosa* • *S. epidermidis* • *S. hominis*
Zimmer[31]	2022	Seven days after FN presentation among single-organism bacteremia: 11 (3.6) 30 days after FN presentation among single-organism bacteremia: 28 (9.3) 30-day mortality general: 33 (9.6)	N/R	Unspecified non-transplant chemotherapy regimens (68%), others (32%) received allogeneic or autologous HSCT	IDSA European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance Clinical Practice Guidelines in Oncology (NCCN)	Cefepime, piperacillin-tazobactam, antipseudomonal carbapenems, meropenem, vancomycin, linezolid, daptomycin, aminoglycosides, beta-lactam	Gram-negative organisms • *E. coli* • *Klebsiella* spp. • *P. aeruginosa* • *E. cloacae* • *Stenotrophomonas* • Other Enterobacterales • Other Gram-negative Gram-positive organisms • Viridans group streptococci • *S. aureus* Oxacillin-resistant Oxacillin-susceptible • Coagulase-negative staphylococci • *Enterococcus* spp. Vancomycin-resistant Vancomycin-susceptible • *Rothia* spp • *S. pneumoniae* • Other Gram-positive Anaerobes

(Continued)

Table 2. (Continued)

Study	Year	Mortality *N* (%)	Febrile neutropenia treatment	Chemotherapy	Febrile neutropenia guideline	Infection management	Isolates found
Perez[32]	2023	In-hospital mortality • Before ASP Intervention: 9 (28.1) • After ASP Intervention: 5 (16.7) • After ASP Intervention Plus BCID2: 11 (35.5) 30-day all-cause hospital readmission ($n = 68$) • Before ASP Intervention: 12 (52.1) • After ASP Intervention: 9 (36) After ASP Intervention Plus BCID2: 7 (35)	N/R	N/R	ESMO IDSA	Drug-resistant strains identified; however, the medications were not named specifically	Gram-positive bacteria • *Staphylococcus* spp. • *S. aureus* • *E. faecium* • *Streptococcus* spp. Gram-negative bacteria • *E. coli* • *K. pneumoniae* • *P. aeruginosa* • *Acinetobacter baumannii* • *C. freundii* • *E. cloacae* • *Acinetobacter lwoffii* • *P. putida* • *A. hydrophila* • *S. marcescens* • *K. oxytoca* • *L. richardii* • *S. maltophilia* • *Proteus* spp. *Candida* spp. • *C. albicans* • *C. tropicalis* • *Candida kefyr*
Schonardie[33]	2023	N/R	N/R	N/R	IDSA ESCMID guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli	Amikacin + colistin, ceftazidime, vancomycin, polymyxins, aminoglycodies, tigecycline	• Fungus • *Coagulase-negative Staphylococcus* • *S. aureus* • *Streptococcus* spp. • Enterococcus spp. • Other Gram-positive bacteria • *E. coli* • *Klebsiella* spp • *Enterobacter* spp • *P. aeruginosa* • *Acinetobacter* app • Other Gram-negative bacteremia

ACCP/SCCM, American College of Chest Physicians/Society of Critical Care Medicine; AGIHO, Infectious Diseases Working Party; ASCO, American Society of Clinical Oncology; ATS, American Thoracic Society; CDC, Centers for Disease Control; CLSI, Clinical and Laboratory Standards Institute; CONS, Coagulase-Negative *Staphylococci* spp.; CTCAE, Common Terminology Criteria for Adverse Events; DGHO, German Society of Hematology and Medical Oncology; ESBL, Extended-Spectrum Beta-Lactamases; ESC, European Society of Cardiology; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESICM, European Society of Intensive Care Medicine; ESMO, European Society for Medical Oncology; GNB, Gram-negative bacilli; GPC, Gram-positive cocci; HNSN, National Healthcare Safety Network; iCHOP, Intensive Care Working Party; IDSA, Infectioius Diseases Society of America; KES Group, *Klebsiella, Enterobacter*, and *Serratia* spp.; MDR, multiple-drug resistance (was defined as nonsusceptibility to ⩾1 agent in ⩾3 antimicrobial categories); MR CONS, Methicillin-resistant Coagulase-Negative *Staphylococci* spp.; MRSA, Methicillin-Resistant *Staphylococcus aureus;* MSSA, Methicillin-susceptible *Staphylococcus aureus*; NCCN, National Comprehensive Cancer Network; SIS, Surgical Infection Society.

for full-text review. Of these, only 22 studies[8,9,15–23,24–34] met the inclusion criteria and were the basis of the qualitative and quantitative analysis (Figure 1).

Characteristics of studies

A total of 22 studies were included for the assessment.[8,9,15–23,24–34] Table 1 describes the author, year of publication, type of study, country, study period, patient population, number of centers, and funding status.

Based on publication year, 14 (63.6%)[15–23,24–26,34,35] studies were published before 2020 and 8 (36.4%)[9,27–33] 2020 and 2023. Geographically, eight studies (36.4%) were from Europe,[8,15,16,18–20,27,29] 6 (27.3%) from South America,[9,17,22,23,32,33] 5 (22.7%) from Asia,[21,24–25,27,34] equivalent to 22.7%; 2 (9.1%) from North America[30,32] and 1 (4.5%) from Oceania.[31] Tables 1 and 2 describe the characteristics of patients with chemotherapy-induced FN with positive blood culture.

Regarding study design, 12 studies (54.5%) were retrospective,[9,15,16,18,21–23,24,25,27,29,33] 8 (36.4%) were prospective,[8,17,19,20,26,28,30,34] 1 (4.5%) was a prospective-retrospective comparison, and 1 (4.5%) was a quasi-experimental pre-post study.[20] Most studies (81.8%, $n=18$) were single center,[15–18,20–23,24,25,27,29,30,32–35] while 5 (22.7%) were multicenter[9,19,26,28,31] (22.7%; Table 1).

Febrile neutropenia definitions were based on guidelines and definitions explicitly referenced by the authors. Four studies (18.2%)[16,22,35] used the Infectious Diseases Society of America (IDSA) definition alone. Sixteen studies (72.7%)[9,18–21,23,24–28,30–34] referenced multiple sources additional to the IDSA guidelines: the 1997 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Unexplained Fever, the 2002 Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer, the European Society for Medical Oncology (ESMO), the fourth European Conference on Infections in Leukemia (2011), the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines, and guidelines for preventing infectious complications in hematopoietic cell transplant recipients. One study (4.5%)[29] did not use the IDSA guidelines, and one (4.5%)[17] did not specify a guideline. Definitions are detailed in Table 1.

Patients with septic shock were reported in three studies (13.6%).[8,20,28] Of these, one study (4.5%)[20] used the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) definition. The remaining two studies (9.1%)[8,28] did not cite a specific sepsis guideline; one article[8] offered a self-defined criterion, and the other[28] provided no definition. Table 2 describes Characteristics of Included Studies on Febrile Neutropenia Treatment, Infection Management, and Table 3 reports the classification of pathogens isolated from positive blood cultures.

Risk of bias

In the risk of bias assessment, two studies (9.1%) presented moderate risk, and twenty studies (90.9%) were classified as low risk (see Supplemental Materials).

Characteristics of patients with post-chemotherapy febrile neutropenia with microorganism identification in blood cultures

A total of 23,319 patients with chemotherapy-induced FN were included, with 8,665 positive blood cultures. The mean age was 48.5 years ± 7.4 years, and the proportion of female patients ranged from 37.8% to 56% across studies.

In 17 studies,[15,17–22,25–26,29–35] all patients ($n=$ 17,960) had only hematologic malignancies. The remaining six studies reported a mixed population, with hematologic malignancy prevalence ranging from 19% to 89% and solid tumors ($n=456$) ranging from 11% to 81%. Severe neutropenia (SNP) was reported in 100% of the patients in 10 studies ($n=3609$).[9,15,17,22,23,27,28,31,33,35] Three studies[16,21,24] reported SNP in 30.2%–52.1% of cases, and one study[16] reported moderate neutropenia in 58.6% of patients.

Neutropenia lasted a median of 2 days (IQR 2–4), up to a maximum of 14 days (IQR 13–19). Notably, Caro et al.[29] reported a median duration of 23 days (IQR 15–38) with fluoroquinolone prophylaxis versus 30 days (IQR 21–51) without.

ICU admission was required in 4.2% to 54.3% of patients.[20,26,32,33,35] Septic shock occurred in 10.2% to 17%,[20,28,35] and vasopressor use ranged from 9.6% to 28.6% in two studies.[23,35] Central venous catheter use was reported in seven

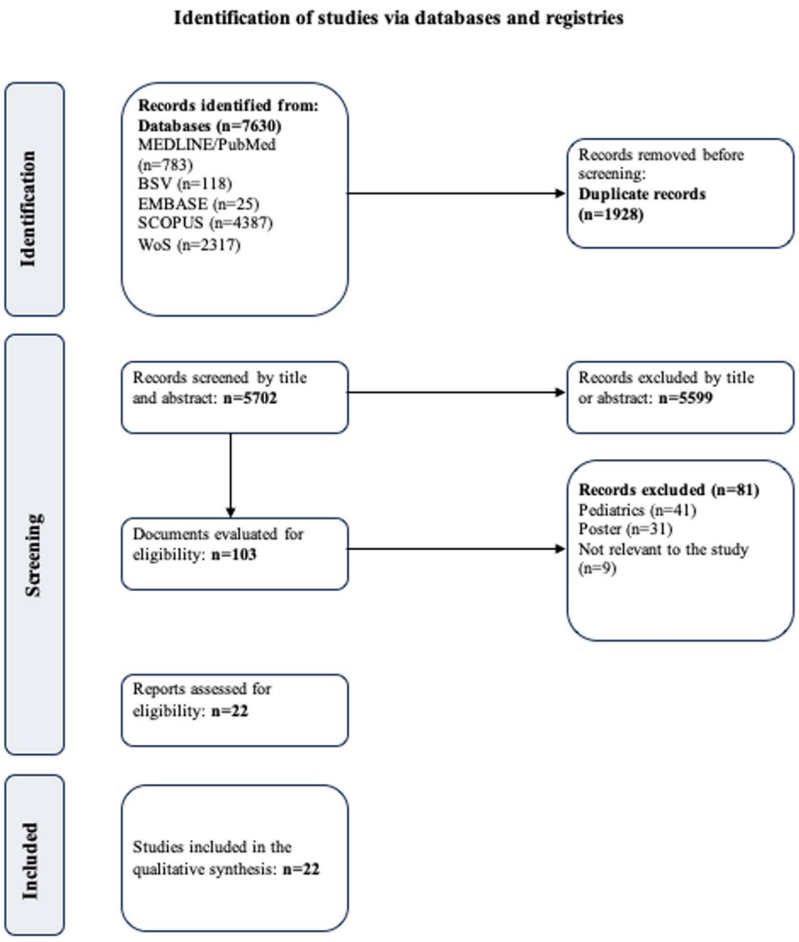

Figure 1. PRISMA flow of selection and exclusion of the information.

studies[9,23,24,27,31,33,35] with a prevalence of 22.9% to 77.9%. Mechanical ventilation was required in 3% to 36.1% across four studies.[20,24,31,33] Reported mortality ranged from 2% to 70%[21] (Table 4).

ICU admission was required in 4.2% to 54.3% of patients.[20,26,32,33,35] Septic shock occurred in 10.2% to mortality ranged from 2% to 70%[21] (Table 4).

Microorganisms identified in blood cultures in a patient with chemotherapy-induced febrile neutropenia

Table 4 summarizes the classification of microorganisms from 8,665 positive blood cultures, Gram-negative bacteria were the most prevalent (46.1%, 95% CI: 45.1–47.2), followed by Gram-positive (42.4%, 95% CI: 41.4–43.5), resistant bacteria (13.4%, 95% CI: 12.4–14.5), and fungi (3.2%, 95% CI: 2.8–3.7).

Among Gram-negatives, the most common were *E. coli* (46.2%, 95% CI: 44.6–47.8), *P. aeruginosa* (18.7%, 95% CI: 17.5–20.0), and *K. pneumoniae* (18.5%, 95% CI: 17.3–19.8) (See Supplemental Material). For Gram-positives, coagulase-negative Staphylococcus with (52.3%, 95% CI: 50.7–53.9), *S. epidermidis* (31.8%, 95% CI: 27.1–37.0), *Enterococcus* spp. (14.7%, 95% CI: 13.4–16.0), and *S. aureus* (9.2%, 95% CI: 8.3–10.1) (see Supplemental Material).

Bacterial resistance was reported in 572 cultures (13.4%), ranging from 3.8% to 100%. Of these, 74.1% (95% CI: 70.1–77.7) were Gram-negative bacteria, while 37.0% (95% CI: 32.5–41.7) were Gram-positive bacteria. The most prominent bacteria were: ESBL-producing *E. coli* (40.4%,

Table 3. Characteristics of patients with chemotherapy-induced FN with positive blood cultures.

Author	Year	Population (*n*)	Age Mean/Median (DS or IQR)	Female gender *n* (%)	Comorbidities *n* (%)	Scales (DS) (IQR)	Type of cancer		Neutropenia			Septic shock *n* (%)	Admission to ICU *n* (%)
							Solid *n* (%)	Hematological *n* (%)	Moderate* *n* (%)	Serious** *n* (%)	Prolonged*** *n* (%)		
De Rosa[15]	2013	81	49.7 (11.4)	35 (43.2)	N/R	N/R	N/R	81 (100)	NR	81 (100)	N/R	N/R	N/R
Bousquet[16]	2014	1413	N/R	N/R	N/R	N/R	N/R	N/R	829 (58.6)	737 (52.1)	N/R	N/R	N/R
Rosa[17]	2014	307	MDR 46.21 (13.0) Others 39.97 (14.2)	149 (48.5)	N/R	N/R	N/R	307 (100)	N/R	307 (100)	N/R	N/R	N/R
Mandal[34]	2015	268	N/R	N/R	N/R	N/R	N/R	268 (100)	N/R	N/R	N/R	N/R	N/R
Marin[35]	2015	510	57 (19–89)	196 (38.4)	Comorbidities: 138 (27.1)	MASCC < 21 152 (31.9%)	N/R	510 (100)	N/R	510 (100)	117 (23.9)	52 (10)	54 (10.6)
Piukovics[18]	2015	469	Medium 60	230 (49)	N/R	N/R	N/R	469 (100)	N/R	N/R	N/R	N/R	N/R
Cattaneo[19]	2016	293	N/R	N/R	N/R	N/R	N/R	293 (100)	N/R	N/R	N/R	N/R	N/R
Rönkkö[20]	2018	178	59 (22–72)	67 (38)	N/R	N/R	N/R	178 (100)	N/R	NR	N/R	15 (11)	6 (4.2)
Zhu[21]	2018	1,065	N/R	N/R	N/R	N/R	N/R	1065 (100)	N/R	322 (30.2)	N/R	N/R	N/R
Garzón[22]	2019	345	50 (33–60)	177 (51.3)	Diabetes mellitus 29 (8.4) Chronic kidney Disease 20 (5.8) Autoimmune diseases 4 (1.2) HIV 10 (2.9)	N/R	N/R	345 (100)	N/R	354 (100)	N/R	N/R	N/R
Herrera[23]	2019	32	53 (18–75)	18 (56)	N/R	N/R	5 (16)	27 (84)	N/R	88 (100)	N/R	N/R	N/R
Kim[24]	2019	179	63.5 (9.8)	79 (44.1)	Liver Cirrhosis 10 (5.6) Diabetes mellitus 51 (11.7) Chronic kidney disease 8 (4.5) Arterial hypertension 51 (28.5)	APACHE 22 (17–29) SOFA 8 (6–11) ECOG 0–1 101 (56.4%) ECOG 2–4 78 (43.6%)	136 (76)	43 (24)	N/R	85 (47.5)	N/R	N/R	N/R
Mert[25]	2019	266	45 (16.5)	111 (41.7)	N/R	N/R	N/R	266 (100)	N/R	N/R	N/R	N/R	N/R
Widmer[26]	2019	13,525	55 (45–63)	5475 (40.5)	N/R	N/R	N/R	13,525 (100)	N/R	N/R	N/R	N/R	539 (4)

(Continued)

Table 3. (Continued)

Author	Year	Population (*n*)	Age Mean/Median (DS or IQR)	Female gender *n* (%)	Comorbidities *n* (%)	Scales (DS) (IQR)	Type of cancer		Neutropenia			Septic shock *n* (%)	Admission to ICU *n* (%)
							Solid *n* (%)	Hematological *n* (%)	Moderate* *n* (%)	Serious** *n* (%)	Prolonged*** *n* (%)		
Jung[27]	2020	133	Unknown cause 60.6 Documented infection 64.3 Documented microbiology 63.6	60 (45.1)	N/R	Unknown cause: APACHE II 18.3 Charlson 6 MASCC 12.1 Documented infection: APACHE II 21.1 Charlson 7.9 MASCC 14.6 Documented Microbiology APACHE II 25.8 Charlson 7.2 MASCC 14.8	108 (81)	25 (19)	N/R	133 (100)	N/R	N/R	N/R
Martinez[28]	2020	1615	58 (45–66)	638 (39)	Diabetes mellitus 158 (10) COPD 104 (6) Liver disease 44 (3) Chronic kidney disease 45 (3)	N/R	179 (11)	1436 (89)	N/R	1615 (100)	N/R	271 (17)	N/R
Finello[9]	2021	143	50 (17.8)	54 (37.8)	Ischemic heart disease 7 (4.9) Diabetes mellitus 11 (7.7) COPD 15 (10.5) Chronic kidney Disease 26 (18.2) Heart failure 9 (6.3) Smoking 42 (29.4)	MASCC 14.5 (±5.5)	28 (20)	115 (80)	N/R	143 (100)	74 (51.7)	N/R	N/R

(Continued)

Table 3. (Continued)

Author	Year	Population (*n*)	Age Mean/Median (DS or IQR)	Female gender *n* (%)	Comorbidities *n* (%)	Scales (DS) (IQR)	Type of cancer		Neutropenia			Septic shock *n* (%)	Admission to ICU *n* (%)
							Solid *n* (%)	Hematological *n* (%)	Moderate* *n* (%)	Serious** *n* (%)	Prolonged*** *n* (%)		
Caro[29]	2022	121	No prophylaxis 62 (52–70) Prophylaxis 64 (52–71)	59 (48.8)	N/R	No prophylaxis: ECOG 0 11 (32.4%) ECOG 1 16 (47.1%) ECOG 2 4 (11.8) Prophylaxis ECOG 0 27 (31%) ECOG 1 31 (35.6%) ECOG 2 12 (13.8%)	N/R	121 (100)	N/R	N/R	N/R	N/R	N/R
Schulz[30]	2022	61	60 (30–77)	27 (44)	N/R	N/R	N/R	61 (100)	N/R	N/R	N/R	N/R	N/R
Zimmer[31]	2022	343	57 (20–89)	145 (42)	N/R	MASCC 19 (5–26) PITT ⩾2 50 (15%)	N/R	343 (100)	N/R	343 (100)	N/R	N/R	N/R
Perez[32]	2023	93	Before PAA 46.7 (38–57.5) After PAA 45.3 (37–56) After PAA 2nd HP 50 (40–62)	50 (53.8)	Diabetes mellitus 4 (4.3) Arterial Hypertension 7 (7.5) HIV 1 (1.1) PeS Heart Failure 1 (1.1) Chronic Kidney Failure 5D 4 (4.3)	MASCC < 21 76 (81.7%)	N/R	93 (100)	N/R	N/R	N/R	N/R	7 (7.5)
Schonardie[33]	2023	35	45.3 (13.6)	17 (48.6)	Cardiovascular 12 (3403) Diabetes Mellitus 3 (8.6) Lung Disease: 3 (8.6) HIV 2 (5.7) Chronic Kidney Failure 2 (5.7)	Charlson 2 (2–3)	N/R	35 (100)	N/R	35 (100)	N/R	N/R	19 (54.3)

APACHE, Acute Physiology and Chronic Health Evaluation; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; HP, positive blood culture; ICU, Intensive Care Unit; IQR, Interquartile Range; MASCC, Risk identification index in neoplastic patients with febrile neutropenia; MDR, Multidrug Resistant; N/R, Not reported; PAA, Antimicrobial stewardship program; PITT, Bacteremia score; SD, Standard Deviation; SOFA, Sepsis-related organ failure assessment.

Table 4. Classification by groups of pathogens isolated in positive blood cultures.

Author	Positive blood cultures (*n*)	GN (*n*)	GN % (95% CI)	GP (*n*)	GP % (95% CI)	Anaerobes (*n*)	Anaerobes % (95% CI)	RB (*n*)	RB % (95% CI)	HP (*n*)	HP % (95% CI)	Fungi (*n*)	Fungi % (95% CI)
De Rosa[15]	79	46	58 (47.1–68.8)	33	42 (31.1–52.8)	N/R	0	3	4 (0.32–8.32)	N/R	0	N/R	0
Bousquet[16]	647	512	79 (75.8–82 1)	135	21 (17.8–24.1)	N/R	0	NR	0	N/R	0	N/R	0
Rosa[17]	39	12	31 (16.4–45.5)	27	69 (54.4–83.5)	N/R	0	37	95 (88.1–100)	N/R	0	N/R	0
Mandal[34]	78	48	62 (51.2–72 7)	27	35 (24.4–45.9)	N/R	0	17	22 (12.8–31.1)	N/R	0	3	3 (0.79–6.79)
Marin[35]	542	273	50 (45.7–54.2)	219	40 (35.8–44.1)	N/R	0	28	5 (3.1–6.8)	50	9 (6.5–11.4)	N/R	0
Piukovics[18]	796	280	35 (31.6 –38.3)	516	65 (61.6–68.3)	N/R	0	N/R	0	N/R	0	N/R	0
Cattaneo[19]	433	166	38 (33.4–42.5)	194	45 (40.3–49.6)	N/R	0	48	11 (8–13.9)	68	15 (11.6–18.3)	5	11 (8–13.9)
Rönkkö[20]	91	26	29 (19.6–38.3)	65	71 (61.6–80.3)	N/R	0	NR	0	N/R	0	N/R	0
Zhu[21]	91	63	69 (59.5–7.5)	28	31 (21.5–40.5)	N/R	0	11	12 (5.3–18.6)	N/R	0	N/R	0
Garzón[22]	403	175	43 (38.1–47.8)	84	21 (17–24.9)	N/R	0	21	5 (2.8–7.1)	142	35 (30.3–39.6)	2	0.4 (0.2–1.0)
Herrera[23]	33	22	67 (50.9–83)	11	33 (16.9–49)	N/R	0	10	30(14.3–45.6)	N/R	0	N/R	0
Kim[24]	23	23	100	NR	0	N/R	0	23	100	N/R	0	N/R	0
Mert[25]	304	232	76 (71.2–80.8)	72	24 (19.2–28.8)	N/R	0	N/R	0	N/R	0	N/R	0
Widmer[26]	2548	759	30 (28.2–31.7)	1647	65 (63.1–66.8)	30	1.1 (0.7–1.5)	N/R	0	N/R	0	112	4.3 (3.5–5)
Jung[27]	109	82	75 (66.8–83.1)	22	20 (12.4–27.5)	5	4.5 (0.6–8.3)	32	29 (20.4–37.5)	N/R	0	N/R	0
Martinez[28]	1736	862	50 (47.6–52.3)	611	35(32.7–-37.2)	41	2.3 (1.5–3)	202	12 (10.4–13.5)	177	10 (8.5–11.4)	45	2.5 (1.7–3.2)
Finello[9]	104	87	84 (76.9–91)	17	16 (8.9–23)	N/R	0	42	40 (30.5–49.4)	N/R	0	N/R	0
Caro[29]	31	12	39 (21.8–56.1)	19	61 (43.8–78.1)	N/R	0	6	19 (5.1–32.8)	N/R	0	N/R	0
Schulz[30]	30	6	20 (5.6–34.3)	9	30 (13.6–46.4)	N/R	0	N/R	0	15	50 (32.1–67.8)	N/R	0
Zimmer[31]	390	183	47 (42–51.9)	190	49 (44–53.9)	17	4.3 (2.2–6.3)	28	7 (4.4–9.5)	N/R	0	N/R	0
Perez[32]	123	93	76 (68.4–83.5)	27	22 (14.6–29.3)	N/R	0	26	21 (13.8–28.2)	N/R	0	3	2.4 (0.3–5.1)
Schonardie[33]	35	35	100	NR	0	N/R	0	35	100	N/R	0	N/R	0

GN, *Gram-negative*; GP, *Gram-positive*; HP, polymicrobial blood cultures; IC, confidence interval; *n*, number; NR, not reported; RB, bacterial resistance.

95% CI: 35.7–45.2), ESBL-producing *Klebsiella* spp. (15.2%, 95% CI: 11.9–19.3), MDR *P. aeruginosa* (22.2%, 95% CI: 18.3–26.7), methicillin-resistant coagulase-negative *Staphylococcus* (47.9%, 95% CI: 39.9–56.0), and MRSA (16.1%, 95% CI: 12.9–20.0) (See Supplemental Material).

Fungal isolations were found in six studies with a prevalence of 3.2% (95% CI: 2.8–3.7). The most frequent were *Candida* spp. (63.8%, 95% CI: 56.1–70.8), *Candida Non-albicans* (36.7%, 95% CI: 28.6–45.6) and *C. Albicans* (14.4%, 95% CI: 9.2–21.9) (see Supplemental Material). In a subgroup analysis, Gram-negative bacteria accounted for 59% (95% CI: 48–70) of bloodstream infections in developed countries (see Supplemental Material). Figures 2 and 3 present the analysis of the prevalence of Gram-positive and Gram-negative bacteria, including subgroup analyses stratified by risk of bias.

In developed countries, fungal pathogens accounted for 2% (95% CI: 1–4) of bloodstream infections (see Figure 4). Risk of bias stratification was not conducted, as all included studies were assessed as low risk.

Source of heterogeneity assessment

In the univariate meta-regression, no significant results were obtained with the covariates: number of participants, risk of bias, and country development status.

Reporting bias

Reporting bias was assessed in studies reporting Gram-negative, Gram-positive, and fungal infections. Egger's test showed *p*-values of 0.17, 0.80, and 0.94, respectively. Although funnel plots showed asymmetry (see Supplemental Materials), the Trim-and-Fill analysis did not impute any missing studies.

Discussion

Cancer patients—especially those with chemotherapy-induced acute leukemia—commonly experience profound and prolonged neutropenia, placing them at high risk for bacteremia and associated mortality. This is the first systematic review summarizing the distribution and characteristics of BSIs in FN patients post-chemotherapy. The primary finding is the high prevalence of both Gram-negative and Gram-positive bacteria and low prevalence of fungal infections.[33]

Since 2000, infections by Gram-negative bacilli have increased, consistent with our finding that they account for 59% of BSIs. Contributing factors may include long-term catheter use, chemotherapy-induced mucositis, and widespread fluoroquinolone prophylaxis.[36] *E. coli*, *K. pneumoniae*, and other Enterobacteriaceae were the most common Gram-negative bacteria.

Gram-positive bacteria were the second most prevalent group. Literature attributes their infections largely to catheters and skin entry points.[37] Our results align with previous studies,[36,38–40] identifying coagulase-negative *Staphylococcus* (52.3%), *S. epidermidis* (31.8%), and *Enterococcus* spp. (14.7%), and *S. aureus* (9.2%).

Gram-negative infections were more frequent in underdeveloped countries than in developed nations.[37,41] This is consistent with findings reported in Latin America, where a BSI prevalence of 38.7% was documented during the 2019–2020 period, with Gram-negative bacteria accounting for 86% of cases. The most frequently identified bacteria were *K. pneumoniae*, *E. coli*, and *P. aeruginosa*.[39] Similarly, a hospital in China reported 62.5% Gram-negative and 33.1% Gram-positive infections from 2012 to 2019.[38] This trend continued in Latin America and Korea from 2020 to 2024, although Gram-positive prevalence is rising globally.

Fungal infections were less common (2%), potentially due to early empirical antifungal treatment in high-risk patients.[41] Diagnostic challenges may also delay detection.[23,44]

Pathogen distribution varies widely across regions,[40] emphasizing the importance of local epidemiology in guiding empirical antibiotic therapy.[41] While bacterial infections remain the primary concern, ongoing surveillance and improved diagnostics are essential for timely management in FN patients.

In infections produced by Gram-positive and Gram-negative organisms, universal quinolone prophylaxis is not recommended for low-risk patients and should be evaluated on a case-by-case basis in high-risk patients. Active monitoring is crucial to detect resistance emergence of resistance.[43]

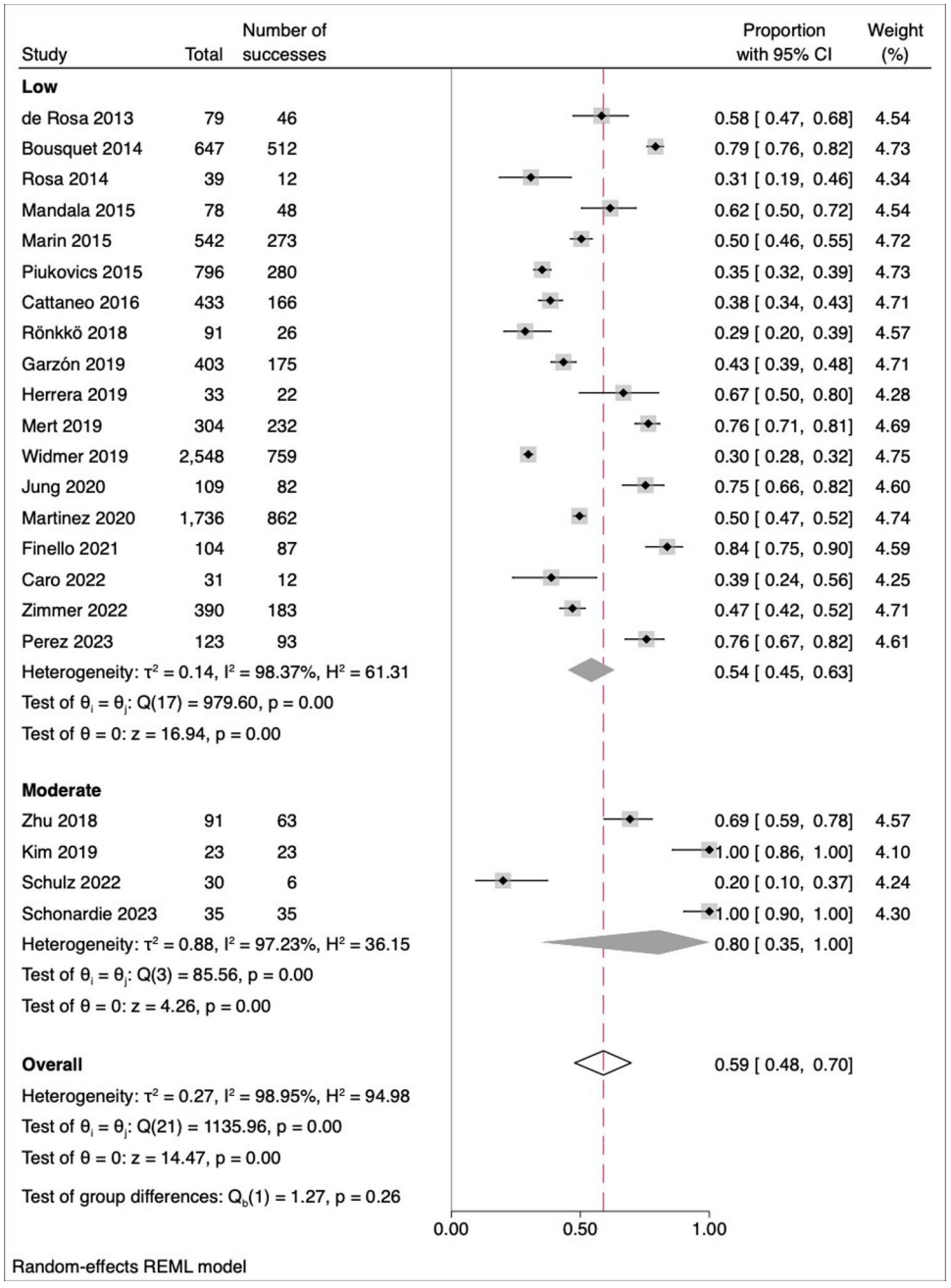

Figure 2. Forest plot of the prevalence of Gram-negative bacteria and subgroup analysis by risk of bias.

Several limitations of our study should be considered. First, most included studies were conducted in a single center, which introduces the possibility of selection and observation biases. Second, not all the studies included report bacterial resistance of the pathogens, which prevents a more complete representation of BSIs caused by resistant microorganisms in this group of patients. Third, patients with and without a central venous catheter as a risk factor for the development of BSI were not compared. Finally, information on predictors and mortality associated with BSI is limited. Despite this, our study provides relevant information on the distribution and characteristics of bloodstream infections in chemotherapy-induced febrile neutropenic patients. Also, there

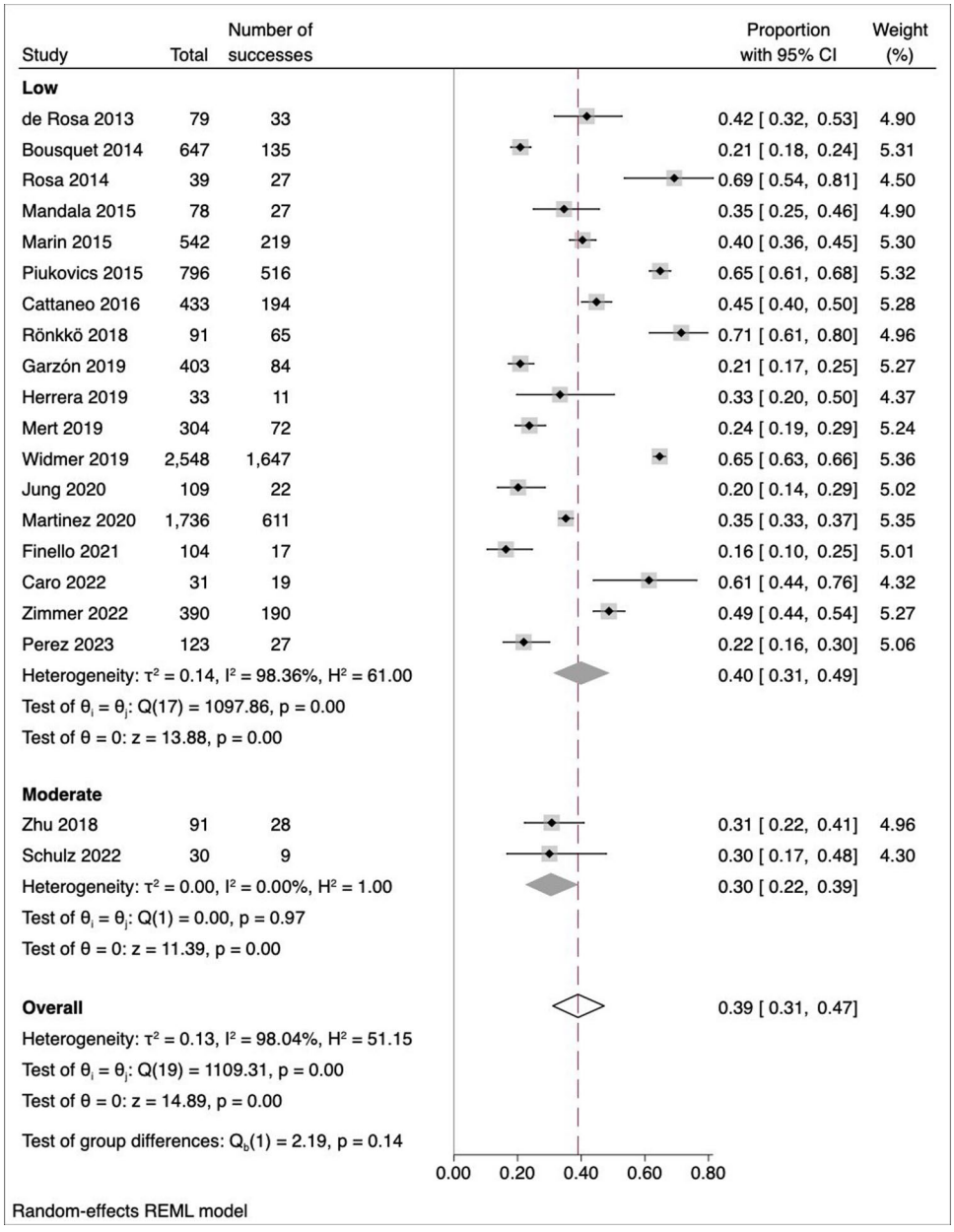

Figure 3. Forest plot of the prevalence of Gram-positive bacteria and subgroup analysis by risk of bias.

is an absence of studies in regions such as Africa and the Middle East.

Conclusion

Cancer patients with post-chemotherapy febrile neutropenia are at high risk for severe infections and mortality. Our analysis revealed a high predominance of Gram-negative (57%) and Gram-positive (39%) bacteria, where *E. Coli* and coagulase-negative *Staphylococcus* as the most common pathogens. Bacterial resistance was observed in 31% of cases, while fungal infections were rare (0.2%).

These findings highlight the importance of ongoing epidemiological surveillance and individualized clinical management to improve outcomes in this high-risk population.

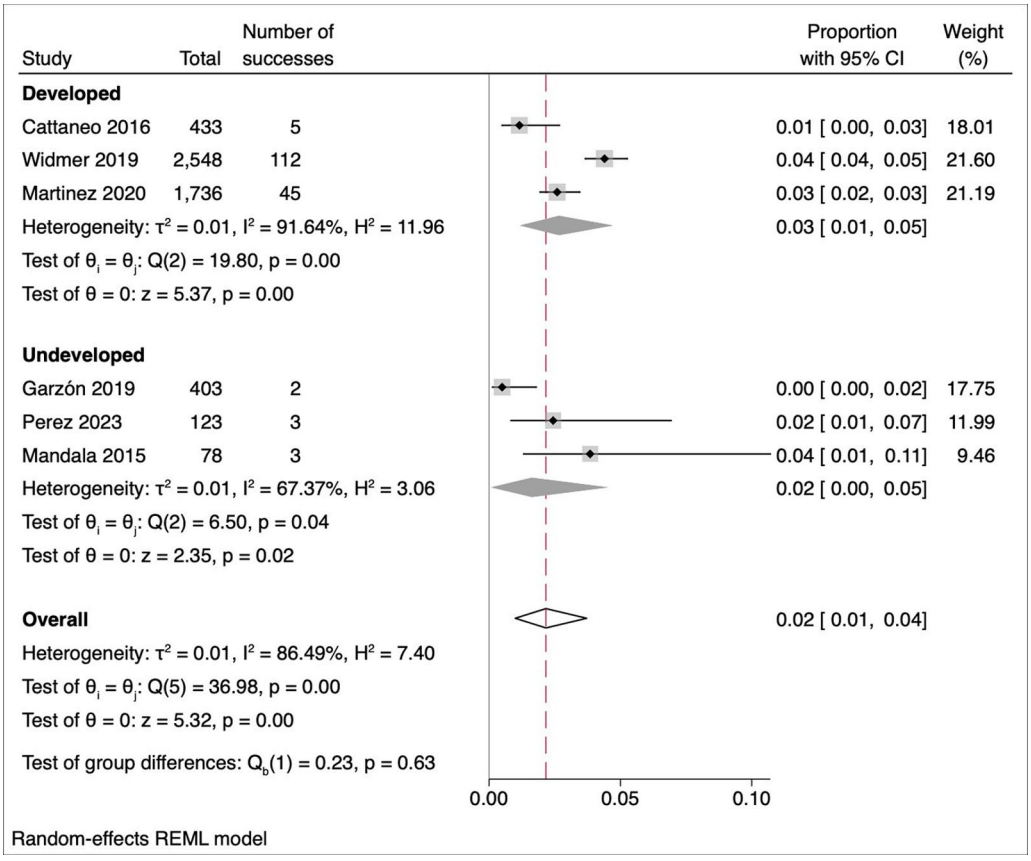
Study
Total
Number of successes
Proportion with 95% CI
Weight (%)
Developed
Cattaneo 2016 433 5 0.01 [0.00, 0.03] 18.01
Widmer 2019 2,548 112 0.04 [0.04, 0.05] 21.60
Martinez 2020 1,736 45 0.03 [0.02, 0.03] 21.19
Heterogeneity: τ² = 0.01, I² = 91.64%, H² = 11.96 0.03 [0.01, 0.05]
Test of θi = θj: Q(2) = 19.80, p = 0.00
Test of θ = 0: z = 5.37, p = 0.00
Undeveloped
Garzón 2019 403 2 0.00 [0.00, 0.02] 17.75
Perez 2023 123 3 0.02 [0.01, 0.07] 11.99
Mandala 2015 78 3 0.04 [0.01, 0.11] 9.46
Heterogeneity: τ² = 0.01, I² = 67.37%, H² = 3.06 0.02 [0.00, 0.05]
Test of θi = θj: Q(2) = 6.50, p = 0.04
Test of θ = 0: z = 2.35, p = 0.02
Overall 0.02 [0.01, 0.04]
Heterogeneity: τ² = 0.01, I² = 86.49%, H² = 7.40
Test of θi = θj: Q(5) = 36.98, p = 0.00
Test of θ = 0: z = 5.32, p = 0.00
Test of group differences: Qb(1) = 0.23, p = 0.63
0.00
0.05
0.10
Random-effects REML model

Figure 4. Forest plot of fungal infection prevalence by World Bank Country Development status.

Declarations

Ethics approval and consent to participate

Systematic reviews are not primary research studies and do not require formal ethical approval. Consent ot participate: Not applicable.

Consent for publication

Not applicable.

Author contributions

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Yunqi Yu Liu: Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Johana Elizabeth Salgado-Apunte: Investigation; Writing – original draft; Writing – review & editing.

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Hernan Sánchez: Formal analysis; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data will be made available upon reasonable request following communication with the corresponding author.

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Supplemental material

Supplemental material for this article is available online.

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Appendix

Abbreviations

FN	Febrile neutropenia
JBI	Joanna Briggs Institute
MeSH	Medical Subject Headings
BSI	Bloodstream Infections
PRISMA	Preferred Statement Reporting Items for Systematic Reviews and Meta-Analysis
COVID	SARS-COV-19
PC	Personal Computer
RoB	Risk of Bias
CI	Confidence Interval
IQR	Interquartile Range
APACHE	Acute Physiology and Chronic Health Evaluation
CCI	Charlson Comorbidity Index
SD	Standard Deviation
ECOG	Eastern Cooperative Oncology Group
HP	Positive blood culture
MASCCv	Risk Identification Index in Neoplastic Patients with Febrile Neutropenia
MDR	Multidrug Resistant
N/R	Not Reported
PAA	Antimicrobial Stewardship Program
PITT	Bacteremia Score
SOFA	Sepsis-related Organ Failure Assessment
IQR	Interquartile Range

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ICU	Intensive Care Unit
HIV	Human Immunodeficiency Virus
DM II	Diabetes Mellitus Type II
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
CKF	Chronic Kidney Failure
CLD	Chronic Lung Disease
IHD	Ischemic Heart Disease
COPD	Chronic Obstructive Pulmonary Disease
HTN	Hypertension
MDR	Multidrug Resistant
XDR	Extensively Drug Resistant
ESBL	Extended-Spectrum Beta-Lactamases